DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-32 and 55, in the reply filed on 7/2/2008 is acknowledged.

2. Claims 33-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/2/2008.

Claim Objections

3. Claims 10-11, 18, 20, 22, 24, 26, and 27 are objected to because of the following informalities:

a. Claim 10 recites, "nuc1eotides," and should read, "nucleotides."

b. Claim 11 is objected to under 37 CFR 1.75(c) as being in improper form because it does not depend from any claim, and therefore the scope of the claim is unclear and cannot be examined. Accordingly, the claim 11 not been further treated on the merits.

c. Claim 18 contains the term, "com prises," which should be one word, comprises.

d. Claim 22 comprises the term, "po11ion(s)," and it appears that it should read, "portion(s)."

e. Claims 20, 24, 26 and 27 contain parenthesis which are unmatched. It is unclear if they are meant to be in the claim or if it is a grammatical error. Appropriate correction is required.

It is also suggested that the applicant review all the claims to fix multiple minor grammatical errors in most of the claims. For instance, claim 4 recites, "said probe is circular probe," which should read, "said probe is a circular probe," and claims 20 and 25 recites, "enzyme acting portion(s)," where there is an extra space before "s."

4. Claims 1-10, 12-32 and 55 are currently under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-10, 12-32, and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is confusing because it cannot be determined what is encompassed by "nearly identical," and the specification does not provide further clarification.

b. Claim 10 is confusing because it is drawn to limitations which are conditional in the claim from which it depends (i.e. claim 7). In further explanation, "the opposite unmodified strand is sensitive to cleavage," is a

limitation that is conditional on the probe being double stranded in claim 7, which is not required by the claim.

c. Claim 17 and 24 are confusing because it cannot be determined what is encompassed by "substantially complementary, "and the specification does not provide further clarification.

d. Claim 22 recites the limitation "the target region(s)" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

e. Claim 22 is confusing because it cannot be determined what is encompassed by "substantially adjacent," and the specification does not provide further clarification.

f. Claim 23 is confusing because it cannot be determined what is encompassed by "wherein said helper primer comprises 3' and 5' target complementary portions, wherein the target region complementary to said probe is located in the middle of the target regions complementary to said helper primer and is adjacent or substantially adjacent to the target regions complementary to said helper primer." The phrase is grammatically confusing as a whole and it is unclear what is meant by the phrase, and therefore, what is required by the claim.

g. Claim 24 is confusing because it is unclear how an enzyme acting portion can be partially functional. Clarification is required.

h. Claim 24 recites the limitation "more than one…of the enzyme acting portions" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

i. Claims 25, 26, and 27 recite the limitation "said enzyme acting portions" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

j. Claim 28 recites the limitation "the circular probe" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

k. Claim 28 recites the limitation "the 5' template portion" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

l. Claim 32 recites the limitation "helper primer" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

m. Claim 55 recites the following limitations which lack antecedent basis:

- "a set of probes" as defined in any one of claims 1 to 32 (i.e. the claims only refer to a probe).
- "said sets of probes" in any one of claims 1 to 32.
- "said helper primers"
- "said detection substrate"
- "said restriction enzymes"
- "said RNA polymerase"
- "said RNase H"
- "said DNA polymerase"

Furthermore, in the last six reciting, "said," it is unclear where the antecedent basis comes from since the claim is an independent claim.

Claim Interpretation

Initially, it is noted that MPEP 2111 states that, "During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. In re Morris, 12'7 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); In re Prater, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969)." As such, for the purposes of examination, particular claims will have the following interpretations:

Claim 1: "wherein said template portion comprises two identical or nearly identical sequences, which are 6 to 300 nucleotides in length and are separated by at least one enzyme acting portion when said probe is linear," is conditional on the probe being linear, therefore, probes which are not linear, and do not have such limitations, still meet the limitations of the claim.

Claim 24: "whereby said target complementary portion of said probe hybridizes to said target region of interest and becomes double stranded," is an intended use of the probe and does not hold patentable weight in the claim. While functional limitations of a product are taken into consideration during examination, patentability cannot rely on the intended use of the probe. See MPEP 2112.01.

Claim 28: "wherein said probe comprises a catalytically inactive antisense sequence complementary to a DNA enzyme in any place of the circular probe *or*

within the 5' template portion with or without surrounding portion sequences of the linear probe," will be interpreted as the probe comprising the antisense sequence in the 5' template region, which includes no other portions of the probe, and therefore, can be any probe sequence which contains such antisense sequences.

Claim 55: Due to the indefiniteness issues mentioned above, for purposes of examination, the claim will be interpreted as a kit comprising a probe as defined in any of one claims 1 to 32, buffers, dNTPs and NTPs.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-5, 17, 19, 22-24, 26, and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Lizardi et al. (US 5,854,033).

Regarding claims 1-3, 5, and 24, Lizardi teaches a probe molecule comprising single stranded or partially double stranded nucleic acid, wherein said probe comprises: a target complementary portion, a template portion, at least one enzyme acting portion, with or without a 3' end block portion and wherein said template portion comprises two identical or nearly identical sequences, which are 6 to 300 nucleotides in length and are separated by at least one enzyme acting portion when said probe is linear (Lizardi

teaches many forms of this probe. Fig.4 and 5, represent the circular and linear forms of the probe, and Figure 5 shows the target probe region (or target complementary portion), promoter region (or enzyme acting portion), and primer complement or secondary targets (either could be referred to as the template portion). In the embodiment that the probe is circular, Lizardi teaches the probe comprising all portions required by the claim (a target complementary portion, a template portion, at least one enzyme acting portion) - see Figure 4 and 5, col.5-9 where it discusses the different portions, and col.9 where it discusses the probe being in circular form). In the embodiment the probe is linear, Lizardi teaches the components of the probe as mentioned above, shown in Fig.5, and also discusses the probe having more than one secondary target portions (i.e. template portions) in the spacer region of the probe, which may have the same sequence (see col.7, lines 49-50) and can be 20 to 70 nucleotides in length (col.7, lines 59-61). Lizardi discusses where the promoter portion can be located anywhere within the spacer region (see col.8, lines 55-56), and therefore, this includes embodiments where the promoter region is between the two identical sequence secondary target portions, satisfying the limitations of claim 1 when it is linear).

Regarding claim 4, Lizardi teaches the probe being circular comprising one template portion (see Fig.4, and col.9 for circular probes, and col.7, lines 40-41, where it discusses that there can be one secondary target portions, or in the embodiment where the primer complement portion is considered the "template portion," see Fig.5 where there is only one primer complement portion (or template portion)).

Regarding claim 17 and 19, Lizardi teaches the probe further comprising a helper primer, wherein said helper primer comprises at least one portion complementary to a part of the probe (see col.10, "Rolling Circle Replication Primer," which hybridizes to the primer complement portion of the probe).

Regarding claims 22-23, Lizardi teaches the probe wherein said helper primer further comprises target complementary portion(s), wherein the target region complementary to said helper primer is adjacent to the target region complementary to said probe (see col.10, lines 16-24).

Regarding claim 26, Lizardi teaches the probe wherein said template portion(s) of said probe comprise modified nucleotides, whereby modified nucleotides are resistant to nuclease cleavage (see col.10, lines 25-28, where it discusses the helper primer having modified nucleotides resistant to nuclease cleavage, and when the helper primer is hybridized to the probe, it creates a partially double-stranded region in the template portion, and therefore can be considered part of the template portion since claim 1 includes probes which are partially double-stranded).

Regarding claim 32, Lizardi discusses where any end of the probe and/or helper primer is attached on a solid support (see col.14, under "K. Solid-State Detection").

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 6, 9-10, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (US 5,854,033) in view of Dattagupta et al. (US 6,596,489).

The teachings of Lizardi et al. are discussed above. Lizardi does not discuss the enzyme acting portion(s) of the probe comprising RNase H acting sequences, Lizardi does not discuss the probe comprising chimeric RNA and DNA.

However, designing probes comprising RNase H acting sequences, as well as both RNA and DNA sequences was conventional in the art at the time of the invention, as shown by Dattagupta et al. (see col.3, lines 2-21, and col.13, lines 36-55).). Therefore, it would have been obvious to one of skill in the art at the time of the invention to modify the probe of Lizardi et al. to include such sequences because Dattagupta demonstrates that it was conventional in the art to design and include such sequences in probes, depending on the desired application. As such, the skilled artisan would have had a reasonable expectation of success to include such sequences in the probe of Lizardi et al. for the intention of probes having various sequences depending on the particular application. It would have been prima facie obvious to one of skill in the art at the time of the invention to make the claimed probe and include such sequences therein.

11. Claims 7-8, 10, 12-16, 20-21, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (US 5,854,033) in view of Jones et al. (US 7,108,976).

The teachings of Lizardi are discussed above. Lizardi does not discuss the probe wherein the enzyme acting portions comprise a type IIs restriction enzyme site, which can comprise modified nucleotides, making it resistant to nuclease cleavage[claims 7-8, 10, 12-13, and 16]. Lizardi does not discuss the probe where the type IIs restriction enzyme cleavage site corresponds to a SNP site, mutations nucleotide, methylation nucleotide, or splicing site [claim 15]. Lizardi also does not discuss the probe wherein the helper primer comprises sequences complementary to the enzyme acting portion, and upon hybridization of the helper primer to the probe, this region becomes double stranded [claims 20-21]. Lizardi does not discuss the probe where the portions either overlap with each other, or have one portion embedded in other portions [claims 14 and 25].

However, designing probes comprising restriction enzyme sequences which support digestion when double-stranded, those comprising modified nucleotides which are resistant to cleavage, and those where the type IIs restriction enzyme site corresponds to a polymorphism site, was conventional in the art at the time of the invention. Additionally probes which further comprise a helper primer that comprises sequences complementary to enzyme acting sequences of the probe, as well as probes where the portions either overlap with each other, or have one portion embedded in other portions, were also well known in the art at the time of the invention, as shown by

Jones et al. (see col.3, lines 36-50). Therefore, it would have been obvious to one of skill in the art at the time of the invention to modify the probe of Lizardi et al. to include such sequences because Jones demonstrates that it was conventional in the art to design and include such sequences in probes, depending on the desired application. As such, the skilled artisan would have had a reasonable expectation of success to include such sequences in the probe of Lizardi et al. for the intention of probes having different enzyme acting sequences depending on the particular application. It would have been prima facie obvious to one of skill in the art at the time of the invention to make the claimed probe and include such sequences therein.

12. Claims 18 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (US 5,854,033) in view of Shafer (US 2004/0053275).

The teachings of Lizardi et al. are discussed above. Lizardi does not discuss the probe wherein the helper primer comprises a 3' end blocking moiety, whereby the 3' end of said helper primer is not extentible by a DNA polymerase [claim 18], or wherein the probe has a 3' block portion [claim 31].

However, it was conventional in the art at the time of the invention to include 3' block portions on primers and probes, as shown by Shafer, depending on the application. Shafer discusses probes with a target complementary portion, two identical template portions, a helper primer, and a 3' block on the probe (see Fig.5, "Double Linker WRAP Probes" and paragraph [0039]).

13. Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (US 5,854,033) in view of Santoro et al., "A general purpose RNA-cleaving DNA enzyme," Proc. Natl. Acad. Sci.,1997, Vol.94, pp.4262-4266.

The teachings of Lizardi et al. are discussed above. Lizardi does not discuss the probe comprising a catalytically inactive antisense sequence complementary to a DNA enzyme in any place of the circular probe or within the 5' template portion with or without surrounding portion sequences of the linear probe.

Santoro discuss probes comprising catalytically inactive antisense sequence complementary to both a 10-23 and 8-17 enzyme in the 5' template portion (see Fig.2 and pg.4263, left column), and therefore, satisfies the limitations of the claim (see claim interpretation).

14. Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (US 5,854,033).

The teachings of Lizardi are discussed above. Lizardi discusses a kit comprising the probes of his invention (see col.19, lines 16-19). Lizardi is silent to whether the kit comprises buffers, dNTPs, an d NTPs. However, since Lizardi demonstrates the benefits of packaging together reagents into a kit for the convenience of practicing methods, and Lizardi discusses the use of buffers, dNTPs and NTPs in methods utilizing the probes of his invention (see Example 2, #2, and #3), one of skill in the art would have been motivated to include such reagents in his kit for the convenience of packaging reagents into a kit. One of skill in the art would have had a reasonable

expectation of success in further including buffers, dNTPs and NTPs in the kit of Lizardi et al. in order to create a kit which comprised all reagents necessary to practice the method of his invention. It would have been prima facie obvious to one of skill in the art at the time of the invention to make the claimed kit and include the claimed reagents therein.

Summary

1. No claims are free of the prior art.
2. The following are noted as references of interest:

   a. Shapero et al. (US 2005/0009059) - Discusses probes with methylation nucleotides at the restriction enzyme type II site, helper primers with promoter sequences and phosphorothioate linkages.

   b. Alajem et al. (WO/01/38570) - Discusses probes which can be double-stranded, where one strand is resistant to cleavage, and 3' blocked probes.

   c. Zhang (US 6,593,086).- Zhang shows probes comprising type IIs restriction enzyme sites and recognition sequences (see Fig.2 and Col.16, lines 40-61), as well as different portions of the probe overlapping with eachother (see Fig.2 and Col.16, lines 40-61).

   d. Winger et al. (US 6,251,600) - Discusses probes comprising chimeric RNA and DNA sequences.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is (571)272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/Molly E Baughman/
Examiner, Art Unit 1637